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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/808,699	NAKADA ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/16/05*. +12/22/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are pending.

2. Upon reconsideration Examiner has extended the search to cover Group V, a method for inhibiting tumor growth comprising administering to the mammal an EMMPRIN antagonist and a second anti-angiogenic agent.

3. Applicant's election with traverse of Group I, claims 1-9 and 15-18 (now 1-9 and 13-18) directed to a method of treating an angiogenesis dependent disease comprising administering to the mammal an EMMPRIN antagonist and a second anti-angiogenic agent, wherein the disease is cancer and angioma as the species filed on 5/5/06, is acknowledged.

Applicant's traversal is on the grounds that the subject matter of Group I-V are all angiogenesis mediated disease and are thus inextricably linked such that they do not constitute independent and distinct inventions as required by the statute. This is not found persuasive because it cannot be seen how an inflammatory disease such as rheumatoid arthritis is not independent **and** distinct form cancer disease such as angioma. Therefore, searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 10-12 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

5. Claims 1-9 and 13-18 are under examination as they read on a method of treating an angiogenesis dependent disease comprising administering to the mammal an EMMPRIN antagonist and a second anti-angiogenic agent, wherein the disease is cancer and a method for inhibiting tumor growth comprising administering to the mammal an EMMPRIN antagonist and a second anti-angiogenic agent, wherein angioma is the species.

6. Applicant's IDS, filed 5/16/05 and 6/26/06, is acknowledged, however, the International Search Report were crossed out but the references listed thereon had been considered. Further the references were crossed out on the IDS filed 6/26/06 because they were duplicates of the references filed on 5/16/05.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma UM-8D6 that produces the CD147-RDI antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

9. Claims 1-9 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating an angiogenesis-dependent disease in a mammal in need thereof comprising administering to the mammal an anti-EMMPRIN antibody in an effective amount to inhibit angiogenesis in said mammal, wherein the angiogenesis-dependent disease is cancer; does not reasonably provide **enablement** for a method for treating any "angiogenesis-dependent disease" in a mammal in need thereof comprising administering to the mammal any "EMMPRIN antagonist" in an amount effective to inhibit angiogenesis in said mammal in claim 1, wherein the antibody fragment is a "derivative

of" Fab, Fab`, or F(ab`)2 fragment in claim 3; or a method for inhibiting tumor growth in a mammal in need thereof comprising administering to the mammal any "EMMPRIN antagonist" in an amount effective to inhibit angiogenesis of the vasculature supporting the growth of said tumor in claim 13, or a method for "preventing" metastases in a mammal in need thereof comprising administering to the mammal an "EMMPRIN antagonist" in an amount effective "prevent metastases" in said mammal in claim 15, wherein the EMMPRIN antagonist is administered in combination with any "second anti-angiogenic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification on page 4, lines 29-33, discloses that an "EMMPRIN antagonist" is capable of preventing the production of EMMPRIN by cells, such as an siRNA or a shRNA molecule or an antibody that specifically binds EMMPRIN.

The specification does not provide a sufficient enabling description of the claimed EMMPRIN antagonist. A person of skill in the art is not enabled to make and use *any* "EMMPRIN antagonist" including "siRNA" or "shRNA" that is capable of preventing the production of EMMPRIN as encompassed by the full breadth of the claims as currently recited. It was well known in the art at the time the invention was made that molecules having highly diverse structural and biochemical properties can function as "antagonists". However, Huang (Pharmacol. Therapeutics 2000 86:201-215) reviews in his "Introduction" on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein-protein interactions, and notes that the process required long periods of trial and error testing before suitable compounds could be developed. Similarly, Toole et al (Storming Media: the role of EMMPRIN in Tumor angiogenesis and metastasis, May 2001) teach that antisense cDNA and ribozyme constructs were utilized in an attempt to inhibit EMMPRIN expression TA3/ST cells, however, these constructs were not efficient in blocking EMMPRIN expression and consequently, were inactive in vivo (see the abstract in particular). Further, Mountain reviews in TIBTECH (18:119-128 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Mountain concludes that it is unlikely that a universal vector will emerge in the next few years (page 125, middle of 1st column). Similarly, although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictablity was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any EMMPRIN antagonist such as a simple or complex organic or inorganic molecule, a peptide, a protein or an oligonucleotide (treatment by 'switching off' genes) are fraught with

uncertainties. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Given the unpredictability associated with identifying individual molecules which would function as "EMMPRIN antagonist" that can inhibit angiogenesis; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim 3, recites antibody fragment derivatives, however, Applicant has not provided sufficient biochemical information that distinctly identifies such "derivatives". While any antibody fragment derivative may have some notion of the activity of the "inhibiting agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such derivatives, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any antibody derivatives that can be used to inhibit angiogenesis mediated disease.

Further, at issue is whether or not the claimed method would function for "preventing tumor growth/metastases". *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. No animal model were used to prevent tumor growth/metastases. Since the method of preventing tumor growth/metastases indices of administering to the animal anti-EMMPRIN antibody can be species- and model-dependent, it is not clear that reliance on the in vitro studies accurately reflects the relative human efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively prevent tumor growth/metastases or reach any therapeutic endpoint in humans by administering anti-EMMPRIN antibodies. The specification does not teach how to extrapolate data obtained from in vitro studies to the development of effective in vivo mammalian including human therapeutic prevention, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the modified blood exemplified in the specification.

However, an effective preventive protocol for the prevention of tumor growth/metastases in mammalian is subject to a number of factors which enter the picture beyond simply the administration of the anti-EMMPRIN antibodies in an acceptable formulation. Demonstrating decrease in the tumor growth/metastases cannot alone support the predictability of the method for preventing tumor growth/metastases through administration of the appropriate formulation. . tumor growth/metastases is subject to variables beyond administration of anti-EMMPRIN antibodies. The ability of a host to suppress and thereby prevent tumor growth/metastases from establishing itself will vary depending upon factors such as the condition of the host and burden of tumor.

Finally, claim 16 recites a combination therapy of the EMMPRIN antagonist with any second anti-angiogenic agent, however, besides thalidomide and anti-alphaV antibodies the specification fails to disclose what other anti-angiogenic agent can be used in the claimed method.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 1-9 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for treating an angiogenesis-dependent disease in a mammal in need thereof comprising administering to the mammal an anti-EMMPRIN antibody in an effective amount to inhibit angiogenesis in said mammal, wherein the angiogenesis-dependent disease is cancer.

Applicant is not in possession of a method for treating any "angiogenesis-dependent disease" in a mammal in need thereof comprising administering to the mammal any "EMMPRIN antagonist" in an amount effective to inhibit angiogenesis in said mammal in claim 1, wherein the antibody fragment is a "derivative of" Fab, Fab`, or F(ab`)2 fragment in claim 3; or a method for inhibiting tumor growth in a mammal in need thereof comprising administering to the mammal any "EMMPRIN antagonist" in an amount effective to inhibit angiogenesis of the vasculature supporting the growth of said tumor in claim 13, or a method for "preventing" metastases in a mammal in need thereof comprising administering to the mammal an "EMMPRIN antagonist" in an amount effective "prevent metastases" in said mammal in claim 15, wherein the EMMPRIN antagonist is administered in combination with any "second anti-angiogenic.

Applicant has disclosed only anti-EMMPRIN antibody as EMMPRIN antagonist and thalidomide and anti-alphaV antibodies as a second anti-angiogenic agent; therefore, the skilled artisan cannot envision all the contemplated EMPRIN antagonist/ anti-angiogenic agent possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-4, 7-8, 13-15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/13763.

The WO `763 publication teaches a method for treating tumor growth or metastasis (angiogenesis-dependent disease) in a patient (human) comprising administering EMMPRIN antagonist such as an anti-EMMPRIN antibody, wherein the antibody is monoclonal antibody, wherein the monoclonal antibody is a Fab and F(ab`)2 fragment, wherein the anti-EMMPRIN antibody binds to an epitope that recognized by the UM-8D6 antib-CD147 monoclonal antibody (see published claims 1-6; page 8, lines 1-17; page 21, line 33 to page 34, line 6; page 26, lines 9-15 and page 57, lines 19-29 in particular), wherein the antibody is administered intravenously (see page 36, line 29 in particular).

The reference teachings anticipate the claimed invention.

13. Claims 1-2, 5, 8, 13-15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Zucker et al (August 2000) (of Record)

Zucker S. teaches a method for treating a mice with EMMPRIN-transfected cancer cells monoclonal antibodies to EMMPRIN. Groups of tumor-bearing mice were treated with saline or 10 mg/kg body weight of antibody twice weekly, tumor size is being measured to determine whether these antibodies have anti-tumor activity (see sum and page 2 in particular). Zucker teaches that the goals of the grant are to demonstrate the role of EMMPRIN in tumor

angiogenesis and perform a structural analysis of EMMPRIN. Zucker teaches that the effect of EMMPRIN on tumorigenesis using EMMPRIN-transfected MDA-MB-436 cells into a mammary tissue. Tumor formation and metastases were recorded during 12 weeks of observation. Major differences in groups were noted. The Tumors derived from the EMMPRIN-GFP cDNA transfected MDA-MB-436 tumor cell injections grew much more rapidly and all 10 mice expired within 12 weeks, intra-abdominal metastases were noted in some mice. Zucker teaches that in contrast, injection of the GFP cDNA alone transfected tumor cells into mice resulted in tumors that grew much more slowly, none of these mice expired and intra-abdominal metastases were noted by termination of the experiment at week 12.

Claim 18 is included because the referenced monoclonal antibodies would compete for binding to human EMMPRIN with the mab CD147-RDI/clone UM8D6 in the absence of evidence to the contrary.

The reference teachings anticipate the claimed invention.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 2, 5-6, 9 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/13763 in view of US. Pat. No. 6,406,693.

The teachings of WO 02/13763 publication have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the monoclonal antibody is administered in the amount of from 0.5-12.o mg/kg body weight in claim 5, or in a bolus dose followed by an infusion of said antibody in claim 6, wherein the disease is angioma in claim 9, in combination with a second anti-angiogenic agent in claim 16, wherein the second anti-angiogenic agent is a Mab capable of specifically binding the adhesion molecules containing alphaV in claim 17.

However, the `693 patent teaches that certain anti-angiogenic therapies have already been shown to cause tumor regressions and that the antibody LM609 also have angiostatic activity. However, in light of their other properties, they are referred to as anti-vascular therapies or tumor vessel toxins, as they not only inhibit angiogenesis but also initiate the destruction of tumor vessels through mostly undefined mechanisms. Their combination with the present invention is clearly envisioned (col., 78, lines 10-64 in particular). Further, the ` 693 patent teaches that the antibody LM609 against αvβ3 integrin also induces tumor regressions. Integrin αvβ3 antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected (see col., 81, lines 8-15 in particular). Finally, the `693 patent teaches the benign tumors, such as angioma (see col., 24, lines 6-7 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the LM609 mab against αvβ3 integrin taught by the `693 patent with the anti-EMMPRIN antibody as taught by the `763 publication in a method for treating an angiogenesis-dependent disease such as tumor growth and metastasis.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody LM609 also have angiostatic activity and LM609 against αvβ3 integrin also induces tumor regressions. Integrin αvβ3 antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected as taught by `693 patent. Further, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

Claims 5-6 are included because the determination of the optimal amount dosage of the antibody is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment , the specific rout of administration and like factors within the knowledge and expertise of the medical practitioner. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 1, 2, 4-9 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zucker et al (August 2000) (of Record) in view of in view of US. Pat. No. 6,406,693.

The teachings of Zucker et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the monoclonal antibody is administered intravenously in claim 4, the monoclonal antibody is administered in the amount of from 0.5-12.o mg/kg body weight in claim 5, or in a bolus dose followed by an infusion of said antibody in claim 6, wherein the mammal is a human in claim 7, wherein the disease is angioma in claim 9, in combination with a second anti-angiogenic agent in claim 16, wherein the second anti-angiogenic agent is a Mab capable of specifically binding the adhesion molecules containing alphaV in claim 17.

However, the `693 patent teaches that certain anti-angiogenic therapies have already been shown to cause tumor regressions and that the antibody LM609 also have angiostatic activity. However, in light of their other properties, they are referred to as anti-vascular therapies or tumor vessel toxins, as they not only inhibit angiogenesis but also initiate the destruction of tumor vessels through mostly undefined mechanisms. Their combination with the present invention is clearly envisioned (col., 78, lines 10-64 in particular). Further, the ` 693 patent teaches that the antibody LM609 against αvβ3 integrin also induces tumor regressions. Integrin αvβ3 antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected (see col., 81, lines 8-15 in particular). Finally, the `693 patent teaches the benign tumors, such as angioma (see col., 24, lines 6-7 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the LM609 mab against αvβ3 integrin taught by `693 patent with the anti-EMMPRIN antibody as taught by Zucker in a method for treating an angiogenesis-dependent disease such as tumor growth and metastasis. Zucker suggests the in vivo, including human, treatment implicitly.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody LM609 also have angiostatic activity and LM609 against αvβ3 integrin also induces tumor regressions. Integrin αvβ3 antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected as taught by `693 patent. Further, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

Claims 5-6 are included because the determination of the optimal amount dosage of the antibody is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment , the specific

rout of administration and like factors within the knowledge and expertise of the medical practitioner. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zucker et al (August 2000) (of Record) in view of in view of Owens *et al* (1994).

The teachings of Zucker et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the monoclonal antibody fragment is Fab, Fab` or F(ab`)2 in claim 3.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Also, antibody fragments are the reagents of choice for some clinical applications (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Zucker et al as Fab and $F(ab')_2$ fragments taught by the Owens *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 1-2, 4-8, 13-15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Looksmart publication 2001 (IDS ref) in view of Sameshima et al (IDS ref.).

Looksmart publication teach the role of EMMPRIN in tumor angiogenesis and metastasis. Looksmart teach that a critical step in tumorigenesis is proteolytic modification of the peri-cellular matrix surrounding tumor cells by matrix metalloproteinases (MMPs). Looksmart teaches that EMMPRIN, a tumor cell surface glycoprotein, stimulates the production of several MMPs by fibroblasts and endothelial cells. Looksmart further teaches that antisense cDNA and ribozyme constructs are utilized in an attempt to inhibit EMMPRIN expression in TA3/ST cells, a murine Brest carcinoma cell line. Looksmart teaches that these constructs are not efficient in blocking EMMPRIN expression and consequently are in active in vivo. However, transfection and injection experiments show that MDA-MB-436 human breast cancer cells transfected with GFP-EMMPRIN can produce much larger tumors in nude mice than vector-transfected cells. Looksmart teaches that EMMPRIN can stimulate the production of MMPs 1,2, and 3 by endothelial cells; MMPs 1, 2 and 3 have been shown previously to promote angiogenesis. Looksmart further teaches that a possible explanation for the increased tumor growth obtained with EMMPRIN-transfected cells is an efficient nutrient supply resulting from angiogenesis. Further, to assay whether EMMPRIN is capable of inducing angiogenesis, HUVECs on type I collagen are treated with either EMMPRIN or bFGF, a known angiogenic factor. As opposed to controls which maintain their cobblestone-like monolayer arrangement, treated HUVECs form capillary-like tubes, lending support to EMMPRIN as an angiogenic factor (see the entire abstract).

Looksmart does not expressly teach the use EMMPRIN monoclonal antibody, but otherwise teaches all of the claimed elements of the claimed method for treating an angiogenesis-dependent disease or inhibiting/preventing tumor growth/metastases in a mammal).

Sameshima et al teach that EMMPRIN is enriched on the surface of tumor cells and stimulates adjacent stormal cells to produce several matrix metalloproteinases (MMPs). Sameshima et al demonstrated that coculturing of EMMPRIN-expressing human glioblastoma multiforme cells (U251) with brain -derived human fibroblasts not only stimulates production, but also activation of pro-gelactinase A (pro MMP-2), an enzyme that is enriched in malignant gliomas and most likely crucial to tumor progression. Sameshima teaches that stimulation of MMP-2, MT1-MMP and MT2-MMP production was inhibited by anti-EMMPRIN monoclonal antibody in a dose-dependent manner (see abstract in particular).

Claim 18 is included because the reference anti-EMMPRIN monoclonal antibody would compete for binding to human EMMPRIN with the monoclonal antibody CD147-RDI/clone UM-8D6 in the absence of evidence to the contrary.

Given that for a new blood vessel to form, endothelial cells from an existing blood vessel must proliferate, cross the basement membrane and migrate into surrounding tissues. In order to do this, endothelial cells must product MMPs. The inhibition of MMP activity has been identified as a means of inhibiting blood vessel formation or angiogenesis. One of ordinary skill in the art

at the time the invention was made would have been motivated to substitute the antisense cDNA or riboszyme constructs therapy for the in vivo use taught by Looksmart article with the anti-EMMPRIN monoclonal antibody taught by Sameshima *et al* because the such antibody inhibited MMPs production which contribute to the angiogenesis. Looksmart suggests the in vivo, including human, treatment implicitly

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because by inhibiting the upstream EMMPRIN effector of MMPs production would lead to the inhibition of angiogenesis and hence tumor growth and metastasis using monoclonal antibody against EMMPRIN.

Claims 4-6 are included because the determination of the optimal amount dosage of the antibody is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment, the specific rout of administration and like factors within the knowledge and expertise of the medical practitioner. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Looksmart publication 2001 (IDS ref) in view of Sameshima et al as applied to claims 1-2, 4-6, 8, 13-15 and 18 above, and further in view of Owens *et al.*

The teachings of Looksmart publication and Sameshima et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the monoclonal antibody fragment is Fab, Fab` or F(ab`)2 in claim 3.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Also, antibody fragments are the reagents of choice for some clinical applications (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Sameshima et al as Fab and $F(ab')_2$ fragments taught by the Owens *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claims 9 and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Looksmart publication 2001 (IDS ref) in view of Sameshima et al as applied to claims 1-2, 4-6, 8, 13-15 and 18 above, and further in view of US. Pat. No. 6,406,693.

The teachings of Looksmart publication and Sameshima et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the angiogenesis-dependent diseases is angioma in claim 9, and that the EMMPRIN antagonist is administered in combination with a second anti-angiogenic agent in claim 16, wherein the second antigiogic agent is a Mab capable of specifically binding the adhesion molecules containing alphaV in claim 17.

However, the `693 patent teaches that certain anti-angiogenic therapies have already been shown to cause tumor regressions and that the antibody LM609 also have angiostatic activity. However, in light of their other properties, they are referred to as anti-vascular therapies or tumor vessel toxins, as they not only inhibit angiogenesis but also initiate the destruction of tumor vessels through mostly undefined mechanisms. Their combination with the present invention is clearly envisioned (col., 78, lines 10-64 in particular). Further, the ` 693 patent teaches that the antibody LM609 against $\alpha v\beta 3$ integrin also induces tumor regressions. Integrin $\alpha v\beta 3$ antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected (see col., 81, lines 8-15 in particular). Finally, the `693 patent teaches the benign tumors, such as angioma (see col., 24, lines 6-7 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the LM609 mab against $\alpha v\beta 3$ integrin taught by the `693 patent with the anti-EMMPRIN antibody as taught by the Sameshima et al in a method for treating an angiogenesis-dependent disease such as tumor growth and metastasis.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody LM609 also have angiostatic activity and LM609 against αvβ3 integrin also induces tumor regressions. Integrin αvβ3 antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected as taught by `693 patent. Further, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 23, 2006

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